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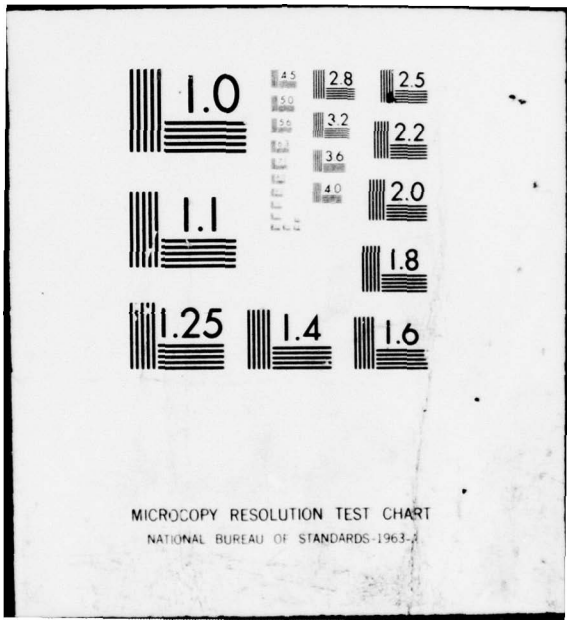
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FACTORS INFLUENCING THE OCCURRENCE OF THE MALIGNANT AND BENIGN CANINE MAMMARY TUMORS

by

Marvin Meinders, DVM

Master's thesis

AFIT-CI-79-58T

Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Department of Epidemiology and Preventive Medicine
School of Veterinary Medicine

UNIVERSITY OF CALIFORNIA, DAVIS
California 95616, U.S.A.

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R. Schneider

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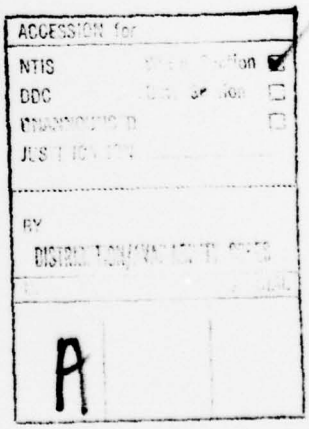
To my wife, Sara Kathryn, who spent many an untiring hour "counting cards" and encouraging me, "I could not have made it without you!"

ABSTRACT

A case control study was used to determine the relationship between the effects of estrus, parity, pseudocyesis, abortion, estrus prevention, and estrus irregularities upon the expression of the benign and malignant forms of the canine mammary tumors.

This study showed that estrus had a more profound influence on the occurrence of the benign than the malignant form of canine mammary tumor, for animals which were neutered experienced 55% of the risk of a benign tumor than their malignant counterpart ($P<.025$). The ability of estrus to set the risk of benign tumor expression seems to be exhibited even after the animal is past the age of maturity. Pregnancy before maturity and pseudocyesis seem to have a subtle effect on the expression of the benign neoplasm through the stimulation of the mixed mammary tumor. Abortion, estrus prevention, and estrus irregularity did not seem to influence either benign or malignant tumors. The factors examined in this study had no predictive value for determining the age at which the neoplasm was expressed.



INTRODUCTION

The mammary tumor is the most common type of neoplasm in the female canine, representing approximately 30% of all tumors diagnosed; but, it is different from most other tumors in this species because it is influenced by sex hormones.[6,12] It also has similarities to the human breast tumor.[9] There is a significant decrease in the risk of mammary tumors in women if they experience an oophorectomy or pregnancy before age 25.[4,5] In the dog, there is a significant decrease in the risk of malignant mammary tumors when the animal is neutered before the age of 2 1/2 years.[6,12] The infiltrating carcinomas of the duct system and lobular carcinomas in the dog represents a close model of human breast cancer in morphology, behavior, and incidence. Histologically benign lesions have been found in the dog mammary tissue. These are morphologically very similar to those recognized commonly in the human breast.[13]

A study by Burns et al [3] stated that there was a significant difference existing in the etiology of benign and malignant breast tumors in humans. Women having malignant breast disease averaged 1.0 years older at birth of first child and 1.6 years older at birth of last child ($P<.001$). Their mothers were more likely to have had a breast cancer (6.8% compared to 4.8% for benign, $P<0.25$). Although both groups reported similar use of birth control pills, malignant cases were less likely to have used hormones for menopausal symptoms. Unpublished studies by Dr. Schneider have indicated that the overall effects of neutering on bitches causes twice the reduced risk of benign verses malignant forms of canine mammary tumors.[11]

This study was undertaken to get a better insight into what may be occurring in malignant and benign expression. It contrasts the effects of

estrus, parity, pseudocyesis, abortion, estrus prevention, and estrus irregularities on the expression of the benign and malignant forms of the canine mammary tumor. The goal was to determine the relationship between these factors and the expression of either the benign or the malignant forms of canine mammary tumors. This information could then be used in the decision making by veterinarians and pet owners in attempting to prevent the disease in the canine.

MATERIALS AND METHODS

A case-control study was conducted using the records form the Alameda-Contra Costa Counties Animal Neoplasm Registry. Histopathologically confirmed malignant and benign mammary tumors were used from the period of July, 1963, to June, 1968. There were approximately 900 mammary tumor cases received in that time period. The owners of 786 of these cases were interviewed in 1970 in order to substantiate and supplement the information on the original tumor submission form.

The data was analysed using the benigns as the case group and the malignancies as the control group. Bitches with malignant neoplasms were matched with bitches with benign neoplasms on the basis of breed and age at the time of tumor diagnosis. Animals with either multiple benign or multiple malignant tumors were considered the same as those with just one tumor represented. Animals with any combinations of both malignant and benign tumors were not used. Matching of age was on the basis of ± 2 years of age at the time of the first tumor diagnosed. Breed matching was on the owner's classification of the individual and its sire and dam. The animal was classified as purebred if the sire and dam were both of the same phenotype. The animal was classified as crossbred it the sire and dam were of two different phenotypes. The animal was classified mixed it it was the progeny of more than two breeds.

The chi-square test for association, student's t-test, and McNemar's test for correlated proportions were used to evaluate the comparative risk of benign or malignant mammary tumor expression for the various test factors. A stepwise multiple regression (BMD/02R) was used to examine the simultaneous influence of a variety of variables upon malignant and benign expression. It was also used in hopes of developing a mathematical equation which would predict the major effects on the age at diagnosis of malignant and benign mammary tumors. The dependent variable was the age of the first tumor diagnosis. A separate run was utilized for the benign and the malignant groups. Each variable was allowed to enter the equation on the value of its F to enter.

In all chi-square tests, the neutered status as of the date of first tumor diagnosis was controlled by using the Mantel-Haenszel procedure except when it was the test category. Cases which were neutered before their first estrus cycle and, therefore, may never have had an influence from sex hormones were not used in this study.

RESULTS

Out of the 786 cases, matching produced 230 pairs of females matched on the basis of age and breed. The distribution of the breeds (Table 1) show that the Dachshund, Poodle, and Cocker Spaniel had the most submissions in that order. A mean ratio of 2.80 ± 1.27 for the occurrence of all benign to malignant neoplasms was found in Registry records for the breeds listed. The Dachshund had a ratio of 1.32 which was the lowest for all breeds represented. The Chihuahua has the highest ratio with 5.64. All other breeds were within one standard deviation of the mean which was considered within the expected variation from normal. In order to preclude a bias in the data due to an over

representation of an extreme breed characteristic, all statistical tests were duplicated with the Dachshund and Chihuahua cases removed. There was no significant difference in any of the statistical tests when these two breeds were removed. Therefore, data presented here includes these two breeds.

Tables 2 and 3 show the effects of the various factors on the expression of the benign mammary tumor.

Effects of Neutering

Cases that were neutered experienced 55% of the risk of having a benign tumor than their malignant counterparts ($P<.025$). There was no statistically significant difference in either group between the occurrence of animals neutered before maturity (≤ 3 years of age) verses those neutered after maturity (Table 2).

Effects of Pseudocyesis and Parity

Bitches experiencing neither a pseudopregnancy nor a pregnancy were used as the reference category. Cases with a history of pseudopregnancy had a 1.85 times greater risk of having a benign neoplasm than cases not experiencing this phenomenon ($P<.10$). Although the risk difference was not significant, this may have been due to the overriding effects of neutering even after adjustment for that factor by the Mantel-Haenszel procedure;since, when using just the cases that were not neutered, the relative risk was 2.30 ($P<.025$). There was no statistically significant difference in the status of parity, multiparity, or age at first pregnancy between the benign and malignant groups (Table 3). However, there was a trend for animals with benign tumors toward having experienced first pregnancy at an earlier age than matched animals of the malignant group. This trend was further

investigated by removing the effects that a large number of litters might have on the age at which the first litter was born. This was accomplished by using only those cases which had given birth to one litter only. Again, there was no statistically significant difference between the age at whelping for the two groups; however, the trend for the benign group to whelp at a younger age continued. The ages at which members of both groups experienced pseudopregnancies were not available; hence, the effect of age of first pseudopregnancy could not be tested.

Effects of Abortion, Estrus Prevention, and Estrus Irregularities

No effects of abortion, estrus prevention, and estrus irregularities were found. However, all three of these test categories were composed of small numbers of cases; thus, the sample size may not have been large enough to detect a subtle difference. Estrus prevention was defined as an animal receiving a pill or injection in order to prevent the clinical symptoms of estrus.

Age at Tumor Diagnosis

Table 4 summarizes the results of the stepwise regression using the age at the time of first tumor diagnosis as the dependent variable. The F ratio for each of the regression equations was not significant. Therefore, the equations would be of no predictive value since there was essentially no difference between the slope of the regression and a horizontal line.

DISCUSSION

The data from this study indicates that there are contrastable factors influencing the expression of the benign and malignant forms of the canine mammary tumor.

Overall, bitches that were neutered experienced 55% of the risk of having a benign tumor than did their malignant counterpart (Table 2). The difference in the expression of the malignant and benign mammary tumors in the neutered animal may be due to an even greater effect of estrus on the benign expression. The mechanism for what is occurring here seems to be that estrus sets the risk for the expression of the mammary tumor; but, when this tumor is expressed it is related to some other event since the variability in the number of estrus cycles only explains approximately 1.3% of the variability of age at tumor diagnosis (Table 4). This event is probably an immunological aging phenomen which was genetically set.[8,10] There was no statistical difference in the risk of benign tumors when testing neutering before maturity verses neutering after maturity and, therefore, would conclude that neutering after maturity is equally as effective as neutering before maturity in reducing the risk of benign tumors. In view that the risk of malignant tumors (control group) is set before maturity and that neutering after maturity does not reduce the risk,[6,12] it seems logical to conclude that even though neutering after maturity reduces risk of benign tumor expression this risk is actually not reduced to as great an extent as would be if neutering occurred before maturity. This conclusion could probably have been substantiated if the benign group had been tested against a normal control group.

The statistical results are not conclusive as to whether pseudocyesis and/or pregnancy has an effect on the expression of the malignant and benign neoplasms. However, this data indicates that both pseudocyesis and pregnancy may have a subtle effect on the expression of the benign tumor; and, in the case of pregnancy, this subtle effect seems to occur when pregnancy is experienced before maturity. Studies by Briggs [1] and Nelson, et al,[7] in trials with contraceptive steroids concluded that progestogens have a

stimulatory effect on the mixed mammary tumor. Mixed mammary tumors comprised 75% of all benign tumors represented in this study. This phenomenon of progestogen stimulation of the mixed mammary tumors could possibly be the explanation for the trend of an increased risk of benign tumors for those animals which experienced either pregnancy before maturity or pseudocyesis. Most other studies in the canine found that these factors had no effect on the occurrence of mammary neoplasms.[2,6,12] However, most other epidemiological studies in animals either did not distinguish between malignant and benign tumors or were conducted using just malignant cases. In man, the incidence of the mixed mammary tumor is rare. If pseudocyesis and pregnancy does stimulate the mixed mammary tumor through the production of certain progestogens, then the large representation of this tumor in the benign group could give an overall effect of increased benign tumor occurrence due to pseudocyesis and pregnancy.

In conclusion, it appears that estrus has a more profound influence on the occurrence of the benign than the malignant form of the canine mammary tumor. The ability of estrus to set the risk of benign tumor expression seems to be exhibited even after the animal is past the age of maturity. Pregnancy and pseudocyesis seem to have a subtle effect through the stimulation of the mixed mammary tumor. The trend in this data for animals of the benign group to experience their first pregnancy before maturity may possibly be a similarity to the human breast tumor where it has been reported that women with malignant tumors averaged one year older at first birth than women with benign tumors;[3] but, further study in this area would be needed to explore this possiblity. Subsequent studies of the relationship between malignant and benign tumors could possibly be improved by using normal animals as controls and/or a larger sample size.

Table 1: Breed Distribution

Breed	Malignant				Benign				Total
	Adeno-carcinoma	Mixed mammary	Other malig	>1 malig	Adenoma	Mixed mammary	Other benign	>1 benign	
Purebred									
Bassett	3					3			6
Beagle	4	3		1		8			16
Boston T.	7					6		1	14
Boxer	6				1	3	2		12
Chihuahua	6	3				8		1	18
Collie	1						1		2
Dachshund	24	14			1	34	3		76
Fox Terrier	2	2				3	1		8
German Shep.	6					3	2	1	12
Kerry Blue T.	1	1				1	1		4
Pekingese	3					3			6
Manchester		1		1		2			4
Pinscher (min)	1					1			2
Pointer (Ger S)	7				1	5	1		14
Pomeranian	1						1		2
Poodle, unspec.	15	16		1	3	24	5		64
Labrador	4	2				5	1		12
Samoyed	1				1				2
Sheltie		2				2			4
Silky T.	1					1			2
Brittany				1		1			2
Cocker	14	2			13	2	1		32
Eng. Springer	2	3			1	3	1		10
Crossbred									
Beagle	1	2				3			6
Boxer	1					1			2
Chihuahua	3	1				4			8
Collie	1	2			1		1	1	6
Dachshund	2					2			4
Fox Terrier	15	3				16	1	1	36
German Shep.	4					3	1		8
Maltese		1			1				2
Pomeranian	1						1		2
Poodle, unspec.	2	1			2	3			6
Cocker	17	3	1			15	3	1	42
Eng. Cocker	1					1			2
Mixed	4	1				5			10
Total	162	63	1	4	25	172	27	6	460

Table 2: Effects of Neutering on the Benign Mammary Tumor.

Benign	Malignant		Relative Risk	Chi Square
	Neutered <3 yrs	Not Neutered		
Neutered ≤3 yrs	3	11	.52	
Not Neutered	21	101		3.13
	Neutered >3 yrs	Not Neutered		
Neutered >3 yrs	1	12		
Not Neutered	21	100	.57	2.45
	Neutered ≤3 yrs	Neutered >3 yrs		
Neutered ≤3 yrs	3	2		
Neutered >3 yrs	1	1	2.00	.33
	Neutered	Not Neutered		
Neutered	7	22		
Not Neutered	40	133	.55	5.23

$X^2 \geq 3.84$ is statistically significant at the 5% level or less. Data analysed using McNemar's test for correlated proportions.

Table 3: The Effects of Factors on the Benign Mammary Tumor.

	Benign	Malignant	Relative Risk	Chi Square
Pseudocyesis	37	21		
vs.				
no pseudocyesis	70	74	1.85	3.75
Parous	74	83		
vs.				
nulliparous	70	74	.98	.01
Age at first litter:				
≤3 yrs	51	51		
vs.				
>3 yrs	11	20	1.89	2.24
EST PVT	23	18		
vs.				
no EST PVT	195	186	1.28	.37
Abortion	12	11		
vs.				
no abortion	207	203	1.09	.02
EST IRREG	14	12		
vs.				
no EST IRREG	150	167	1.20	.37
Age at birth for uniparous:				
≤3 yrs.	17	14		
vs.				
>3 yrs	8	16	2.36	2.42

$X^2 \geq 3.84$ is statistically significant at the 5% level or less. Neutered status controlled for by using the Mantel-Haenszel procedure.

EST PVT = estrus prevention
EST IRREG = estrus irregularity

Table 4: The Effects of the Variables Upon Age of Tumor Diagnosis.

Malignant

$$\text{Age tumor diagnosed} = 9.03 + .03\ X_1^{*} - 1.74X_2 + 1.18X_3 - .86X_4$$

$$F \text{ ratio} = 1.23^{ns}$$
$$R^2 = .0431$$
$$F_{.95;4,110} = 2.46$$

Benign

$$\text{Age tumor diagnosed} = 8.88 + .03X_1^{**} - .68X_2 + .07X_5$$

$$F \text{ ratio} = 1.11^{ns}$$
$$R^2 = .0291$$
$$F_{.95;3,126} = 2.68$$

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*Was the first variable entered with R^2=.0122
**Was the first variable entered with R^2=.0139
X_1 = number of estrus
X_2 = number of litters whelped by one year of age
X_3 = number of litters whelped by two years of age
X_4 = number of litters at 2.5 years of age
X_5 = number of pseudocyesis

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